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Florbetapir F18 PET Amyloid Neuroimaging and Characteristics in Patients With Mild and Moderate Alzheimer Dementia

Elisabeth K. Degenhardt, R.N., M.S.N., Michael M. Witte, Ph.D., Michael G. Case, M.S., Peng Yu, Ph.D., David B. Henley, M.D., Helen M. Hochstetler, Pharm.D., Deborah N. D'Souza, Ph.D., M.B.A., Paula T. Trzepacz, M.D.

Background: *Clinical diagnosis of Alzheimer disease (AD) is challenging, with a 70.9%–87.3% sensitivity and 44.3%–70.8% specificity, compared with autopsy diagnosis. Florbetapir F18 positron emission tomography (FBP-PET) estimates beta-amyloid plaque density antemortem.* **Methods:** *Of 2052 patients (≥55 years old) clinically diagnosed with mild or moderate AD dementia from 2 solanezumab clinical trials, 390 opted to participate in a FBP-PET study addendum. We analyzed baseline prerandomization characteristics.*

Results: *A total of 22.4% had negative FBP-PET scans, whereas 72.5% of mild and 86.9% of moderate AD patients had positive results. No baseline clinical variable reliably differentiated negative from positive FBP-PET scan groups.* **Conclusions:** *These data confirm the challenges of correctly diagnosing AD without using biomarkers. FBP-PET can aid AD dementia differential diagnosis by detecting amyloid pathology antemortem, even when the diagnosis of AD is made by expert clinicians.*

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INTRODUCTION

Accurate diagnosis of the causes of cognitive impairment allows physicians, patients, and patients' families to manage treatments for the underlying disorder(s) and develop a more focused plan for future psychosocial and medical needs.[1–4] Additionally, patients appreciate receiving the diagnosis.[5] Among the top 4 causes for dementia, Alzheimer disease (AD) is the most common followed by vascular, Lewy body, and frontotemporal dementias.[6] The clinical diagnosis of AD is challenging and often not made in a timely fashion, especially by primary care physicians who may wait for several years to make and communicate the diagnosis to those affected and their family members, in part, due to uncertainty.[7–9] Care must be taken to include a thorough assessment of signs and symptoms, as well as central nervous system and medical conditions known to cause or mimic dementia. Blood tests and structural (head computerized tomography (CT) or magnetic resonance imaging (MRI)) and functional positron emission tomography (PET) neuroimaging using fluorodeoxyglucose (FDG)-PET are commonly used during differential

Received December 22, 2014; revised November 30, 2015; accepted December 1, 2015. From IU Health Physicians Group, Department of Psychiatry, Indiana University School of Medicine Collaboration, Indiana University Health, Indianapolis, IN (EKD); Lilly USA, LLC, Neurosciences, Indianapolis, IN (MMW, DBH, HMH); Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN (MGC); Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN (DBH, PTT); inVentiv Health, LLC, Burlington, MA (DNDS). Send correspondence and reprint requests to Helen Hochstetler, Pharm.D., Lilly USA, LLC, Lilly Corporate Center, DC 5021, Indianapolis, IN 46285; e-mail: hochstetler_helen_m@lilly.com

diagnosis, along with neuropsychologic testing. Cerebrospinal fluid (CSF) measurement of soluble AD biomarkers for soluble amyloid-beta (β) and tau is clinically available, but results are not widely standardized and patient acceptance of lumbar puncture varies. Newer PET technology that detects β-amyloid plaque in the living brain is more recently increasing in availability and use. Tau PET is under development and not yet ready for use in clinical practice.

β-Amyloid neuropathologic changes characteristic of AD occur decades before the first clinical symptoms appear.[10,11] A number of medications currently in development for potential disease modification target the amyloid cascade. In addition, the field is moving toward making and communicating an accurate diagnosis of AD earlier, as it may decrease medical costs,[12] help families understand the need for intervention and support, and increase the likelihood for patient involvement in future decisions about, for example, their health care, finances, and other life plans.[13]

Clinically, the diagnosis of AD dementia is made by assessing cognitive, language, and functional abilities using the International Classification of Diseases, tenth revision (ICD-10), Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV), and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS/ADRDA) criteria.[14] However, a definitive diagnosis of AD is made only by neuropathologic examination, at autopsy or rarely with brain biopsy. When data from the National Alzheimer Coordinating Center were analyzed to determine accuracy of a clinical diagnosis for possible or probable AD dementia vs neuropathologic findings characteristic of AD at autopsy, sensitivity ranged from 70.9%–87.3% and specificity ranged from 44.3%–70.8%, depending on the levels of clinical and neuropathologic criteria used.[15] In 82 elderly patients in the OPTIMA study, the agreement between clinical and final cliniconeuropathologic diagnosis using the Consortium to Establish a Registry for Alzheimer Disease was substantial ($\kappa = 0.7$), when possible and probable AD categories were combined.[16]

Because knowledge about the clinical manifestations and biology of AD has increased considerably, the long-standing NINCDS/ADRDA criteria for AD were revised in 2011. Changes were made in the clinical criteria for diagnosis, and biomarker evidence was integrated into the diagnostic formulations for probable and possible AD dementia for use in research settings.[17] Suggested biomarkers include those from 2 categories: β-amyloid related including CSF Aβ-1-42 levels and amyloid PET neuroimaging, and neurodegeneration including CSF-tau and phospho-tau levels, FDG-PET, MRI. The apolipoprotein E ε4 genotype (*APOE4*) is the most robust genetic risk factor for sporadic late-onset AD, but it is not an absolute predictor even in patients with *APOE4* homozygote status who are at very high risk to develop AD.[18]

A total of 3 PET radiotracers for β-amyloid plaque detection are currently approved by the Food and Drug Administration, including florbetapir F18 (FBP) PET, as a diagnostic tool for patients with cognitive impairment suspected of having AD.[19,20] FBP-PET visual interpretation and quantitative estimates of cortical amyloid plaques correlated with the presence and quantity of β-amyloid pathology at autopsy, respectively.[19] FBP can be used to distinguish individuals with sparse to no amyloid plaques from those with moderate to frequent amyloid plaques using a visual binary interpretation of the PET scan.[21] The FBP-PET positive or negative scans have also been defined in research using a cutoff on the standardized uptake value ratio (SUVR), a quantitative analysis of the ratio of cortical to cerebellar signal.[21,22]

We report a *post hoc* analysis of patients with a clinical diagnosis of mild or moderate probable AD dementia by dementia experts who participated in biomarker substudies in 2 registration clinical trials of solanezumab. We investigated whether prerandomization clinical characteristics, cognitive, neuropsychiatric, or functional scores differed between patients with or without clinically significant β-amyloid plaque deposition as measured with FBP-PET. The purpose was to ascertain whether any clinically available characteristics could have reliably distinguished the amyloid status of patients.

MATERIAL AND METHODS

Patients and Design

Study data are for a subset of patients ($n = 390$) among 2052 patients from 2 nearly identical solanezumab registration trials[23] pooled for this cross-sectional, *post hoc* analysis. Patients in this report were ≥ 55

years, clinically diagnosed with mild or moderate AD dementia and opted to participate in an FBP-PET scan study addendum at sites with PET imaging centers. Demographic, cognitive, neuropsychiatric, genetic, and FBP-PET images were obtained at baseline before randomization to drug. Amyloid positivity was not a study entry criterion. Both trials had identical entry criteria and enrolled medically stable male and female patients with probable AD per NINCDS/ADRDA criteria.[24] Inclusion criteria were the following: Modified Hachinski Ischemia Scale ≤ 4, Geriatric Depression Scale (GDS) short form ≤ 6, and Mini-Mental State Examination (MMSE) between 16 and 26 inclusive. Other inclusion criteria were MRI or CT scan performed within the previous 2 years with no findings inconsistent with a diagnosis of AD. Patients were permitted to be on concurrent medications for AD if they had been on the medication for at least 4 months and at a stable dose for at least 2 months before study randomization. About 89% of patients were taking cholinesterase inhibitors (such as donepezil, galantamine, rivastigmine, or tacrine) with or without memantine at the time of study entry. Our trial designs defined mild AD dementia as MMSE scores of 20–26 (inclusive) and moderate as MMSE 16–19.[23]

All patients and caregivers provided written informed consent according to the Declaration of Helsinki, and the study procedures were approved by the institutional review boards. A complete description of the primary studies can be found in Doody et al.[23]

Neuropsychiatric and Functional Assessment

Various assessment tools including measures of cognition, global functioning, and psychopathology were administered at baseline. The Alzheimer Disease Assessment Scale-Cognitive Subscale, 14-item version (ADAS-Cog14)[25,26] measures dysfunction in cognitive domains, such as orientation, verbal memory, language, praxis, and executive function. The score ranges from 0–90, with higher scores indicating greater impairment. The Alzheimer Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Inventory,[27] (ADCS-ADL) is a 23-item scale that assesses eating, bathing, walking, reading, shopping, and managing money. Scores range from 0–78, with higher scores indicating greater independence in the performance of activities of daily living (ADLs). The Clinical Dementia Rating–Sum of Boxes (CDR-SB)[28] evaluates cognition and functional performance in 6 domains including memory, orientation, judgment and problem solving, home and hobbies, community affairs, and personal care. The scores in each of the 6 areas are summed to yield CDR-SB scores ranging from 0–18, in which higher scores indicate more severe impairment. The MMSE[29] is a multidomain office-based cognitive test that assesses orientation, memory, attention, visuoconstructional ability, naming, and the ability to follow written and oral commands with scores ranging from 0 (very impaired)–30 (normal). The Neuropsychiatric Inventory (NPI)-12[30] measures frequency and severity of psychopathology in neurologically-impaired patients including delusion, hallucination, agitation or aggression, apathy, anxiety, depression, euphoria, irritability or lability, disinhibition, aberrant motor behavior, and neurovegetative changes, such as appetite and nighttime behavior disturbances. Scores range from 0 (mild)–144 (severe). The NPI subscales for agitation or aggression, frontal symptoms, and mood symptoms have been validated using principal component analysis.[31] The GDS[32] is a 15-item measure for depressive symptoms with scores ranging from 0–15 (more symptoms), in which a 7-point cutoff indicates syndromal depression.

FBP-PET Neuroimaging

At baseline before drug randomization, PET neuroimaging was performed after the intravenous administration of 370 MBq of F18-FBP. Images were obtained and emission data were collected, corrected for attenuation, and reconstructed using the 3-dimensional maximum *a priori* method specified in the studies' protocols.[23] The SUVR was calculated as the ratio of the mean of 6 cortical regions of interest (frontal, temporal, precuneus, parietal, anterior cingulate, and posterior cingulate), relative to the whole cerebellum reference region with a threshold for amyloid positivity of >1.10.[19,21,22]

Laboratory Analyses

APOE4 genotype was determined as a part of the serum biochemical measurements and hematologic

analyses used in the original trials to analyze for effects of *APOE4* carrier status.

Statistical Analyses

All statistical analyses were performed using SAS 9.2 (Cary, NC). Descriptive statistics used means and standard deviations. Demographic, rating scale, genetic (APOE4 status), and cognitive data were compared by either 2-tailed Fisher's exact test (for categorical variables) or analysis of variance (ANOVA, for continuous variables) between patients categorized as positive or negative for β-amyloid on FBP-PET. This comparison was conducted separately for 3 groups of patients: all patient, patients with mild AD dementia, and patients with moderate AD dementia. Pearson correlations were performed between composite SUVR with age and years of education for the entire cohort. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic Characteristics

Of 390 mild and moderate probable AD dementia patients, 87 (22.4%) were found to be FBP-PET negative (Table). The negative scan group had a significantly lower proportion of females (43.7% vs 56.3%; $p = 0.0145$) than the positive scan group. Baseline age and education were similar between the scan groups, though disease duration since onset of symptoms was significantly longer in the positive group ($p = 0.0056$).

Positive FBP-PET scans occurred in 72.5% of the mild vs 86.9% of the moderate AD dementia group ($p = 0.0014$). In the mild group, those with negative scans were significantly younger than those with positive ($p = 0.0051$).

Clinical Characteristics

There was less severe cognitive impairment in the negative compared with positive scan group as indicated by mean ADAS-Cog14 (28.2 ± 12.1 vs 35.2 ± 10.7; $p < 0.0001$) and MMSE scores (22.2 ± 3.1 vs 20.5 ± 3.0; $p < 0.0001$).

MMSE scores were significantly different between scan groups only in the mild dementia group ($p = 0.0005$). Among the MMSE domains, orientation and recall were significantly worse in the amyloid-positive group ($p < 0.0001$ and $p = 0.0003$), again driven by the mild dementia group. Similar to MMSE, the only difference for ADAS-Cog14 was in the mild dementia group where those with negative scans had significantly better scores than those with positive scans ($p < 0.0001$).

More years of education ($r = 0.1835$; $p = 0.0003$), but not age ($r = 0.0388$; $p = 0.4449$), correlated significantly with higher FBP-PET SUVR indicating amyloid burden.

A significantly smaller proportion of the negative scan group was *APOE4* carriers (22.62% vs 62.85%; $p < 0.001$). Homozygotes for the *APOE4* allele were highly likely to be amyloid positive (mild = 100.00%, moderate = 95.83%).

No differences were found between positive and negative scan groups or their mild AD subgroups on ADCS-ADL, CDR-SB, NPI, or GDS.

DISCUSSION

We retrospectively analyzed pooled clinical and FBP-PET scan data from baseline visits for 390 clinical trial patients who had been clinically diagnosed as having mild or moderate probable AD dementia. About one-fifth (22.4%) of patients did not have evidence of β-amyloid plaque pathology despite having received a clinical diagnosis of AD by expert physicians participating in therapeutic clinical trials. Considering only the mild dementia cases, 27.5% had negative FBP-PET scans, consistent with the literature that earlier phases of AD are more difficult to diagnose accurately. Though clinically evaluated before enrollment to rule out other causes for their cognitive impairment (e.g., vascular dementia, Parkinson's disease, major depression), these patients who are amyloid-negative presented with the AD clinical phenotype yet lacked sufficient β-amyloid plaque density on FBP-PET scans to support their AD diagnosis. The cause of their dementia is not known as part of this research but possibilities include tauopathies, frontotemporal dementia, and hippocampal sclerosis.

It is possible to have false-positive or false-negative PET scan results, though the pivotal FBP-PET registration trials showed very high concordance with AD neuropathologic autopsy diagnoses, including 96% sensitivity and 100% specificity in those

TABLE. Comparison of Baseline Variables Between Positive FBP-PET and Negative FBP-PET Scan Groups, with Values by Dementia Stage Subgroup ($N = 390$)

Variable	Positive FBP-PET[*] $n = 303$ (mild = 182, moderate = 119) Mean (SD)	Negative FBP-PET[*] $n = 87$ (mild = 69, moderate = 18) Mean (SD)	p Value[†]
Duration of diagnosis (years)	2.38 (1.92)	2.06 (1.88)	0.1804
Mild	2.14 (1.82)	1.68 (1.57)	0.0659
Moderate	2.75 (2.02)	3.54 (2.26)	0.1304
Duration of disease onset (years)	**4.75 (2.55)**	**3.92 (2.06)**	**0.0056**
Mild	**4.55 (2.43)**	**3.70 (2.08)**	**0.0107**
Moderate	5.09 (2.71)	4.78 (1.81)	0.6367
Years of formal education	13.13 (3.64)	12.32 (4.73)	0.0888
Mild	13.54 (3.28)	12.78 (4.62)	0.1464
Moderate	12.49 (4.07)	10.56 (4.87)	0.0699
Modified Hachinski Ischemia Scale	0.69 (0.76)	0.84 (0.85)	0.1077
Mild	0.66 (0.74)	0.84 (0.88)	0.1022
Moderate	0.71 (0.76)	0.83 (0.71)	0.5063
Age (years)	75.23 (8.37)	73.25 (9.14)	0.0587
Mild	**75.26 (8.41)**	**71.81 (9.17)**	**0.0051**
Moderate	75.25 (8.35)	78.78 (6.76)	0.0900
ADAS-Cog14	**35.23 (10.65)**	**28.16 (12.09)**	**<0.0001**
Mild	**31.73 (9.83)**	**24.22 (8.52)**	**<0.0001**
Moderate	40.44 (9.71)	43.28 (12.01)	0.2646
CDR-SB	5.02 (2.13)	4.68 (2.83)[‡]	0.2256
Mild	4.43 (1.67)	3.93 (2.25)	0.0555
Moderate	**5.89 (2.42)**	**7.53 (3.04)**	**0.0111**
ADCS-ADL	60.83 (11.11)	59.57 (15.31)	0.3986
Mild	63.30 (10.19)	63.14 (13.35)	0.9205
Moderate	**57.13 (11.51)**	**45.89 (14.92)**	**0.0003**
ADCS-ADL instrumental	39.96 (9.86)	39.53 (13.15)	0.7398
Mild	42.23 (9.01)	42.54 (11.72)	0.8262
Moderate	**36.61 (10.18)**	**28.00 (12.16)**	**0.0014**
ADCS-ADL basic	**20.84 (2.10)**	**20.02 (2.98)**	**0.0040**
Mild	21.04 (2.02)	20.61 (2.24)	0.1406
Moderate	**20.51 (2.19)**	**17.78 (4.26)**	**<0.0001**
NPI—12	8.8 (10.37)[§]	7.63 (12.14)	0.3724
Mild	7.64 (9.70)	6.86 (10.50)	0.5764
Moderate	10.52 (11.13)	10.61 (17.11)	0.9765
NPI-4 agitation subscale	2.78 (4.97)[§]	1.87 (3.76)	0.1143
Mild	2.47 (4.87)	1.71 (3.18)	0.2310
Moderate	3.30 (5.14)	2.50 (5.54)	0.5420
NPI-3 mood subscale	2.95 (4.66)	2.41 (4.82)	0.3482
Mild	2.35 (3.53)	2.26 (4.28)	0.8723
Moderate	3.88 (5.92)	3.00 (6.61)	0.5629
NPI-4 frontal subscale	2.90 (4.26)	2.47 (4.02)	0.3978
Mild	2.73 (4.34)	2.20 (3.72)	0.3772
Moderate	3.14 (4.13)	3.50 (5.00)	0.7403
MMSE	**20.48 (3.01)**	**22.21 (3.07)**	**<0.0001**
Mild	**22.54 (1.86)**	**23.48 (1.91)**	**0.0005**
Moderate	17.43 (1.19)	17.33 (1.19)	0.7521
MMSE attention and calculation	2.67 (1.66)	2.82 (1.55)	0.4627
Mild	3.20 (1.57)	3.07 (1.53)	0.5523

TABLE. Continued

Variable	Positive FBP-PET* $n = 303$ (mild = 182, moderate = 119) Mean (SD)	Negative FBP-PET* $n = 87$ (mild = 69, moderate = 18) Mean (SD)	p Value†
Moderate	1.87 (1.47)	1.83 (1.25)	0.9116
MMSE language	7.86 (1.06)	8.07 (1.07)	0.1022
Mild	8.08 (0.93)	8.26 (0.92)	0.1736
Moderate	7.52 (1.16)	7.33 (1.28)	0.5280
MMSE orientation	**6.36 (1.99)**	**7.45 (2.10)**	**<0.0001**
Mild	**7.14 (1.75)**	**8.06 (1.59)**	**0.0002**
Moderate	5.19 (1.78)	5.11 (2.19)	0.8597
MMSE registration	2.92 (0.32)	2.89 (0.32)	0.3188
Mild	2.96 (0.25)	2.88 (0.32)	0.0645
Moderate	2.88 (0.39)	2.89 (0.32)	0.9467
MMSE recall	**0.78 (0.98)**	**1.22 (1.03)**	**0.0003**
Mild	**0.98 (1.06)**	**1.36 (1.04)**	**0.0107**
Moderate	0.48 (0.76)	0.67 (0.77)	0.3297
GDS	1.76 (1.45)	1.99 (1.60)	0.1987
Mild	1.86 (1.47)	1.90 (1.58)	0.8454
Moderate	**1.58 (1.40)**	**2.33 (1.64)**	**0.0394**
FBP-PET SUVR Composite	**1.45 (0.20)**	**0.96 (0.08)**	**<0.0001**
Mild	**1.45 (0.20)**	**0.96 (0.08)**	**<0.0001**
Moderate	**1.46 (0.19)**	**0.94 (0.06)**	**<0.0001**
APOE4 positive carrier status, *n* (%)			
Mild and moderate	**181 (62.85)**	**19 (22.62)**	**<0.0001**
Mild	**106 (62.35)**	**16 (24.24)**	**<0.0001**
Moderate	**73 (62.93)**	**3 (16.67)**	**<0.0001**
APOE4 alleles, *n* (%)			
Mild			
0	**64 (37.65)**	**50 (75.76)**	**<0.0001**
1	**83 (48.82)**	**16 (24.24)**	**<0.0001**
2	**23 (13.53)**	**0 (0.00)**	**<0.0001**
Moderate			
0	**43 (37.07)**	**15 (83.33)**	**0.0013**
1	**50 (43.10)**	**2 (11.11)**	**0.0013**
2	**23 (19.83)**	**1 (5.56)**	**0.0013**

ADAS-Cog14 = Alzheimer Disease Assessment Scale-Cognitive Subscale, 14-item version; ADCS-ADL = Alzheimer Disease Cooperative Study Activities of Daily Living Inventory; *APOE4* = apolipoprotein E-ε4 alleles; CDR-SB = Clinical Dementia Rating–Sum of Boxes; FBP-PET = florbetapir-fluorine-18 positron emission tomography; GDS = Geriatric Depression Scale—short form; MMSE = Mini-Mental State Examination; NPI = Neuro Psychiatric Inventory; SD = standard deviation; SUVR = standardized uptake value ratio.

* FBP-PET scans were categorized as either positive or negative for the presence of abnormal levels of amyloid neuritic plaque using a cutoff value of 1.1.

† Frequencies are analyzed using Fisher's exact test, means by analysis of variance. Bold font indicates significant values. Significance set at $p < 0.05$.

‡ $n = 86$.

§ $n = 302$.

whose scans were performed within the year before autopsy.[19,21]

Patients who are amyloid-negative with probable AD have been reported in other AD clinical trials where amyloid biomarkers have been used. In the IDENTITY phase 3 study program using semagacestat and similar entry criteria, 18% of patients with clinically diagnosed probable mild or moderate AD

dementia who had an FBP-PET scan were amyloid-negative, where 24% of the mild dementia cases were negative.[33] In bapineuzumab clinical trials, negative-amyloid PET scans (using C11-Pittsburgh Compound-B (PiB)) were found in 22.4% of placebo completers in phase 3 clinical registration trials and 16% in phase 1b clinical trials.[34–36]

Similar to Witte et al.,[33] we did not find any clinical characteristic that could reliably predict amyloid status even though some had statistically significant differences— such as disease duration. Neuropsychiatric symptoms, including depression, mood, agitation or aggression, and frontal symptoms, did not differ between any of the groups. In the mild group, the patients who are amyloid-negative were less cognitively impaired and somewhat younger (early 70s) than the amyloid positive, without functional differences. MMSE domains for recall and orientation were significantly less impaired in the amyloid-negative mild group. Interestingly, in the moderate group, functional impairment was greater in negative than positive patients for both basic and instrumental ADLs. Though these differences are interesting, they do not form a pattern that could on its own elucidate the underlying cause for negative-amyloid cases. Antemortem tests may not exist yet for some of the causes to be considered. *APOE4* genotype is a well-known risk factor for AD and amyloid deposition, though these are not synonymous.[37,38] Chiao et al.[35] found that 23% of *APOE4* carriers were amyloid-negative compared with 57% of noncarriers. Salloway et al.[36] reported that a greater number of *APOE4* noncarriers were PiB-PET negative (36.1%) compared with *APOE4* carriers (6.5%). Witte et al.[33] also reported that negative FBP-PET scans were more common in *APOE4* noncarriers (82%) than carriers (18%). Similarly, we found fewer *APOE4* carriers in the FBP-PET negative vs the positive group (22.62% vs 62.85%), and homozygotes for the *APOE4* allele were highly likely to be FBP-PET positive (97.92%). In a clinically diagnosed patient, *APOE4* homozygosity could be potentially useful in place of amyloid PET. Patients in the study were diagnosed clinically with AD using robust inclusion and exclusion criteria. Although not all patients had amyloid PET scans, among those who did, a positive scan in combination with the clinical diagnosis should result in a high likelihood of AD.

One limitation of our report is that only a subset (390 of 2052) patients from 2 large registration trials were represented in this analysis, which may not be generalizable to the community population. However, these data do replicate prior findings by others in which up to 18.0% of patients[33] diagnosed with AD by dementia specialists did not have supportive evidence on amyloid PET.[39]

The 2 characteristic neuropathologic findings of AD are β-amyloid plaques and neurofibrillary tangles, which are aggregates of abnormal forms of tau. Although recent developments in tau PET imaging have made it possible to visualize tau accumulation in parts of the brain characteristic for AD, this technology is still under development and was not available in our studies. In this study, CSF levels of tau were not considered because they were only measured in a subset of patients[23] and not in all of the patients in the amyloid PET imaging group. Additionally, by the time of the dementia stage of AD, neurofibrillary tangle pathology is likely to be present along with β-amyloid plaque. Therefore, making use of tau imaging or measurement of CSF-tau is of little benefit to this particular study design.

Reliable differential clinical diagnosis in dementia would be helpful in communicating the course and prognosis to patients and families, identifying AD patients for clinical trials and in making appropriate treatment decisions.[14] Amyloid PET imaging is a validated and approved adjunctive biomarker in the diagnosis of AD. Our report and that of others form an emerging literature demonstrating that phenotype and a thorough but conventional dementia work-up cannot alone accurately diagnose AD antemortem, especially during earlier disease phases.

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References

1. Rasmusson DX, Brandt J, Steele C, Hedreen JC, Troncoso JC, Folstein MF: Accuracy of clinical diagnosis of Alzheimer's disease and clinical features of patients with non-Alzheimer's disease neuropathology. Alzheimer Dis Assoc Disord 1996; 10(4):180–188
2. Pearl GS: Diagnosis of Alzheimer's disease in a community hospital-based brain bank program. South Med J 1997; 90(7): 720–722
3. Nagy Z, Esiri MM, Hindley NJ, et al: Accuracy of clinical operational diagnostic criteria for Alzheimer's disease in relation to different pathological diagnostic protocols. Dement Geriatr Cogn Disord 1998; 9(4):219–226
4. Petrovitch H, White LR, Ross GW, et al: Accuracy of clinical criteria for AD in the Honolulu-Asia Aging Study, a population-based study. Neurology 2001; 57(2):226–234
5. Mastwyk M, Ames D, Ellis KA, Chiu E, Dow B: Disclosing a dementia diagnosis: what do patients and family consider important? Int Psychogeriatr 2014; 26(8):1263–1272
6. Hsiung GR: Epidemiology of Alzheimer's disease and dementia. in Feldman HH, editor. Atlas of Alzheimer's Disease. London: Informa UK Ltd; 2007
7. Speechly CM, Bridges-Webb C, Passmore E: The pathway to dementia diagnosis. Med J Aust 2008; 189(9): 487–489
8. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H: Missed and delayed diagnosis of dementia in primary care: Prevalence and contributing factors. Alzheimer Dis Assoc Disord 2009; 23:306–314
9. Leung KK, Finlay J, Silvius JL, et al: Pathways to diagnosis: exploring the experiences of problem recognition and obtaining a dementia diagnosis among Anglo-Canadians. Health Soc Care Community 2011; 19(4): 372–381
10. Villemagne VL, Burnham S, Bourgeat P, et al: Australian Imaging Biomarkers and Lifestyle (AIBL) research group (2013). Amyloid β deposition, neurodegeneration and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013; 12: 357–367
11. Jack CR Jr., Knopman DS, Jagust WJ, et al: Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013; 12:207–216
12. Geldmacher DS, Kirson NY, Birnbaum HG, Eapen S, Kantor E, Cummings AK, Joish VN: Implications of early treatment among Medicaid patients with Alzheimer's disease. Alzheimers Dement 2014; 10:214–224
13. Johnson KA, Minoshima S, Bohnen NI, et al: Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. Alzheimers Dement 2013; 9:e-1–16
14. Genius J, Klafki H, Benninghoff J, Essellman H, Wiltfang J: Current application of neurochemical biomarkers in the prediction and differential diagnosis of Alzheimer's disease and other neurodegenerative dementias. Eur Arch Psychiatry Clin Neurosci 2012; 262(2 Suppl):S71–S77
15. Beach TG, Monsell SE, Phillips LE, Kukull W: Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. J Neuropathol Exp Neurol 2012; 71:266–273
16. Hogervorst E, Barnetson L, Jobst KA, et al: Diagnosing dementia: interrater reliability assessment and accuracy of the NINCDS/ADRDA criteria versus CERAD histopathological criteria for Alzheimer's disease. Dement Geriatr Cogn Disord 2000; 11:107–113
17. McKhann GM, Knopman DS, Chertkow H, et al: The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 263–269
18. Cacabelos R: Genomic characterization of Alzheimer's disease and genotype-related phenotypic analysis of biological markers in dementia. Pharmacogenomics 2004; 5: 1049–1105
19. Clark CM, Schneider JA, Bedell BJ, et al: Use of florbetapir-PET for imaging beta-amyloid pathology. J Am Med Assoc 2011; 305:275–283
20. Full prescribing Florbetapir F18 Injection for intravenous use. Eli Lilly. Silver Spring, MD, Food and Drug Administration, 12/2013.
21. Joshi AD, Pontecorvo MJ, Clark CM, et al: Performance characteristics of amyloid PET with florbetapir F18 in patients with Alzheimer's disease and cognitively normal subjects. J Nucl Med 2012; 53:378–384
22. Clark CM, Pontecorvo MJ, Beach TG, et al: Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-beta plaques: a prospective cohort study. Lancet Neurol 2012; 11:669–678
23. Doody RS, Thomas RG, Farlow M, et al: Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370:311–321
24. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939–944
25. Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984; 141:1356–1364
26. Mohs RC, Knopman D, Petersen RC, et al: Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. Alzheimer Dis Assoc Disord 1997; 11(2 Suppl):S13–S21
27. Galasko D, Bennett D, Sano M, et al: An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997; 11(2 Suppl): S33–S39

28. NACC Clinical Dementia Rating. Available from: http://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER1_2/guide.pd; 2006. Accessed January 9, 2014.
29. Folstein MF, Folstein SE, McHugh PR: Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198
30. Cummings JL, Mega M, Gray K, et al: The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308–2314
31. Trzepacz PT, Saykin A, Yu P, et al: Alzheimer's Disease Neuroimaging Initiative. Subscale validation of the neuropsychiatric inventory questionnaire: comparison of Alzheimer's disease neuroimaging initiative and national Alzheimer's coordinating center cohorts. Am J Geriatr Psychiatry 2013; 21:607–622
32. Sheikh JI, Yesavage JA: Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986; 5:165–173
33. Witte M, Trzepacz P, Case M, et al: Association between clinical measures and florbetapir F18 PET neuroimaging in mild or moderate Alzheimer's disease. J Neuropsychiatry Clin Neurosci 2014; 26(3):214–220
34. Sperling R, Salloway S, Raskind M, et al: Bapineuzumab Phase 3 trials in mild to moderate Alzheimer's disease dementia in apolipoprotein E e4 carriers (Study 302) and non-carriers (Study 301). Electronic resource. Available from: http://www.ctad.fr/07-download/Congres2012/Press Release/Final-Sperling-CTAD-Presentation-10-29-12.pdf. Accessed February 11, 2013.
35. Chiao P, Suhy J, Barakos J, et al: P18 – Amyloid PET screening results by APOE E4 status from a phase 1B clinical study 221AD103 in prodromal to mild AD patients. J Nutr Health Aging 2013; 17:824
36. Salloway S, Sperling R, Fox NC, et al: Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med 2014; 370:322–333
37. Green RC, Roberts JS, Cupples LA, et al: Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med 2009; 361:245–254
38. Roberts JS, Christensen KD, Green RC: Using Alzheimer's disease as a model for genetic risk disclosure: Implications for personal genomics. Clin Genet 2011; 80:407–414
39. Fleisher AS, Chen K, Liu X, et al: Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. Arch Neurol 2011; 68:1404–1411